



To Investigate the Clinical Effect of Sodium Hyaluronate Injection Combined With Zhengqing Fengtongning Injection in the Treatment of Knee Osteoarthritis

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Keywords

Knee osteoarthritis; Sodium hyaluronate injection; Zhengqing Fengtongning injection; Intra-articular injection; Clinical efficacy

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Abstract

Objective: To investigate the effect of sodium hyaluronate injection combined with Zhengqing Fengtongning injection in the treatment of knee osteoarthritis.

Methods: A total of 68 patients with knee osteoarthritis admitted to the Department of Acupuncture and Moxibustion of Yueyang Baixin Orthopedic Hospital from June 2024 to June 2025 were collected as the research objects. According to the digital random method, they were divided into the control group and the observation group, with 34 cases in each group. The control group was treated with sodium hyaluronate injection, and the observation group was treated with sodium hyaluronate injection combined with Zhengqing Fengtongning injection. The curative effect, knee joint function, pain and stiffness were compared between the two groups before treatment and 1, 2 and 3 weeks after treatment.

Results: Compared before treatment, the WOMAC score and VAS score of the two groups were significantly reduced at each time point after treatment ($P < 0.05$), and the decrease of WOMAC score in the observation group was significantly greater than that in the control group ($P < 0.05$). The improvement of each dimension and total score of SF-36 quality of life in the observation group was significantly better than that in the control group 3 weeks after treatment ($P < 0.05$). The total effective rate of the observation group was 91.18%, which was significantly higher than 73.53% of the control group ($P < 0.05$). During the treatment, there were no serious adverse reactions in the two groups, and only a few patients had slight injection site discomfort, which was relieved by themselves.

Conclusion: Sodium hyaluronate injection combined with Zhengqing Fengtongning injection in the treatment of knee osteoarthritis can effectively relieve knee joint pain, improve joint function and quality of life, and has good safety, which is worthy of further clinical application.

Introduction

Osteoarthritis (OA) is a whole joint and heterogeneous disease. Articular cartilage damage is the main pathological change, which can involve synovium, ligaments, subchondral bone and surrounding bone tissue. Knee joint is the most commonly involved joint [1] in OA. Knee osteoarthritis (KOA) is mainly characterized by pain, stiffness and limited movement of the affected joint, and some patients are accompanied by joint swelling, anxiety, depression and sleep disorders, which eventually lead to decreased quality of life and physical disability [1]. From 1990 to 2019, the global prevalence of KOA has increased by 48% [2]. KOA affects nearly 100 million people worldwide and causes 18.9 million years lived with disability (YLD), accounting for 2.2% of the global burden of all diseases, making it the fourth leading cause of disability [3]. The prevalence of symptomatic KOA in China is 8.1%, and YLD is 1.97 million person-years, which is higher in females than in males. It has become one [4,5] of the most common

diseases causing disability. The high morbidity and disability rate of KOA has caused a huge economic burden [6] to patients, families and society. Non-surgical treatment of KOA is an important part of early and basic treatment. Standardized non-surgical treatment measures can help to control symptoms and delay disease progression, so as to avoid late joint replacement surgery as much as possible, so as to reduce the burden [7,8] on patients' health and economy.

Drug therapy is throughout the whole process of KOA treatment. Clinicians need to take early, individualized and targeted treatment strategies according to the patient's condition, needs and preferences, refer to the mechanism of drug action and evidence-based medicine, and fully consider the adverse reactions of drugs, so as to achieve scientific and rational drug [1] use.

Hyaluronic acid can stimulate the endogenous synthesis of hyaluronic acid and extracellular matrix components by synovial fibroblasts, promote cartilage protection by reducing proteoglycan loss in cartilage and chondrocyte apoptosis, and also reduce the degradation of

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hyaluronic acid by reducing the production of proinflammatory cytokines, and reduce the induction [9] of pain mediators. A large amount of evidence has confirmed that Intra-articular injection of hyaluronic acid (IAHA) can not only relieve pain, but also delay the progression [10] of KOA with its potential disease improvement effect. A meta-analysis investigating the safety of IAHA in the treatment of KOA has shown that IAHA is safe [11] for symptomatic KOA patients.

Sinomenine, the main component of Zhengqing Fengtongning, has analgesic, anti-inflammatory and immunomodulatory effects. A systematic review and meta-analysis of the efficacy and safety of Zhengqing Fengtongning in the treatment of KOA showed that Zhengqing Fengtongning in the treatment of KOA could reduce joint pain (SMD=-0.87, 95%CI -1.08 -- 0.66) and improve joint stiffness (SMD=-0.53, 95%CI -1.08 -- 0.66). 95%CI -0.86 -- 0.20) and joint function (SMD=-0.76, 95%CI -0.97 -- 0.55) [12].

Although both drugs used alone have some efficacy, it has been found in clinical practice that some patients have no significant improvement in symptoms after single drug.

However, there are few studies on the combination of sodium hyaluronate and Zhengqing Fengtongning in the treatment of KOA, especially the lack of large sample, randomized controlled trials to verify their synergistic effect. The aim of this study is to investigate the clinical efficacy and safety of the combined intra-articular injection of sodium hyaluronate and Zhenqifongning in the treatment of KOA through a randomized controlled trial, so as to provide new ideas and basis for clinical treatment.

Materials and methods

General Information

A total of 68 patients with knee osteoarthritis treated in the Department of Acupuncture and Moxibustion of Yueyang Baoxin Orthopedic Hospital from June 2024 to June 2025 were selected as the research objects. According to the digital random method, they were divided into the control group and the observation group, with 34 cases in each group. Diagnostic criteria: (1) recurrent knee pain within the past month; (2) age ≥ 50 years old; (3) morning stiffness ≤ 30 minutes; (4) bone fricatives during activities; (5) X-ray films (standing or weight-bearing position) showed narrowing of the joint space, sclerosis or cystic degeneration of the subchondral bone, and osteophytes formation at the edge of the joint. The diagnosis can be made if 1+ any 2 other signs are met. According to the diagnostic criteria [13] of "Chinese Guidelines for the Diagnosis and Treatment of Osteoarthritis (2024 edition)". Inclusion criteria: patients who met the above diagnostic criteria and did not take other treatment or other drugs within one month. Exclusion criteria: (1) allergic to sodium hyaluronate or Zhengqing Fengtothenin; (2) patients with serious heart, liver, kidney and other important organ diseases; (3) with knee infection, tumor, tuberculosis and other knee joint diseases; (4) patients received intra-articular drug injection or similar treatment within 1 month before enrollment; (5) pregnant or lactating women.

Treatment Methods

Control group: the patient was placed in the supine position, the knee was naturally flexed 90° , and the conventional disinfection drape was used to determine the puncture point of the outer superior edge of the patella (located at the intersection of the lateral patellar ligament and the edge of the patella). Using a 5ml syringe, the needle (specification: 22G) was inserted slowly. When the needle tip entered the joint cavity, the

syringe was withdrawn to confirm that there was no blood or abnormal secretion, and then 2ml sodium hyaluronate injection (specification: 2ml:20mg, manufacturer: Shanghai Haohai Biological Technology Co., LTD., Chinese medicine approval character Chinese medicine approval character H20051837) was slowly injected into the joint cavity. After the injection, pull out the needle, cover the puncture point with sterile gauze, and press gently for a moment to avoid drug spillage. The injection was given once a week, and 3 consecutive injections were taken as a course of treatment.

The observation group was treated with Zhengqing Fengtongning injection on the basis of the control group. The patient's position, puncture point location and disinfection drape steps were the same as those of the control group. After the needle entered the joint cavity and was pulled back to confirm that it was correct, 2ml sodium hyaluronate injection was injected first, and then 2ml Zhengqing Fengtongning injection (specification: 2ml:50mg, manufacturer: Hunan Zhengqing Group Co., LTD., Sinopuncture approval number Z43020279) was injected. After the injection, the same sterile gauze was used to cover the puncture point and press. The injection frequency and course of treatment were the same as those of the control group, once a week for 3 consecutive times.

Patients in both groups were instructed to avoid strenuous exercise, keep their knee joints warm, and avoid water at the puncture site within 24 hours after treatment to reduce the risk of infection. At the same time, other drugs for knee diseases were not allowed to be used during the treatment, so as not to affect the accuracy of the study results.

Observation Indicators

(1) Pain assessment; Including VAS and WOMAC pain scale; (2) Functional assessment: WOMAC function scale was used; (3) SF-36 quality of life scale was used for evaluation. (4) drug compliance and safety evaluation [14-16].

Statistical methods

SPSS 22.0 was used for analysis, and measurement data were expressed as (mean $\pm$ standard deviation). Independent sample t test was used for inter-group comparison, and paired t test was used for intra-group comparison. Count data were analyzed by χ^2 test. $P < 0.05$ was considered statistically significant.

Results

Table 1. Comparison of baseline data between the two groups before treatment

Baseline Measures	Control group (n=34)	Observation group (n=34)	t/ χ^2 value	P value
Age (years)	62.35 $\pm$ 7.28	61.89 $\pm$ 6.95	0.298	0.766
Gender (male/female)	12/22	14/20	0.367	0.545
Duration of illness (months)	45.67 $\pm$ 12.34	47.21 $\pm$ 11.89	0.582	0.562
WOMAC total score (points)	67.19 $\pm$ 7.35	67.32 $\pm$ 7.28	0.072	0.943
VAS score (points)	7.25 $\pm$ 1.23	7.31 $\pm$ 1.19	0.201	0.841

Table 2. Comparison of WOMAC scores between the two groups before and after treatment (mean $\pm$ standard deviation, scores)

Time	Groups	Number of cases	Pain score	Stiffness score	Functional rating	Total score
Before treatment	Control group	34	18.25 $\pm$ 3.12	6.58 $\pm$ 1.23	42.36 $\pm$ 5.47	67.19 $\pm$ 7.35
	Observation group	34	18.19 $\pm$ 3.08	6.62 $\pm$ 1.19	42.51 $\pm$ 5.39	67.32 $\pm$ 7.28
1 week after treatment	Control group	34	14.56 * 2.87 mm	5.21 * 1.05 mm	35.67 * 4.89 mm	55.44 * 6.54 mm
	Observation group	34	12.34 $\pm$ 2.56 * #	4.12 $\pm$ 0.92 * #	31.25 $\pm$ 4.32 * #	47.71 $\pm$ 5.86 * #
2 weeks after treatment	Control group	34	11.89 * 2.45 mm	4.35 * 0.87 mm	29.78 * 4.12 mm	46.02 * 5.78 mm
	Observation group	34	9.21 $\pm$ 2.13 * #	3.25 $\pm$ 0.76 * #	25.46 $\pm$ 3.87 * #	37.92 $\pm$ 5.12 * #
3 weeks after treatment	Control group	34	9.56 * 2.01 mm	3.56 * 0.72 mm	24.32 * 3.56 mm	37.44 * 4.89 mm
	Observation group	34	6.89 $\pm$ 1.87 * #	2.34 $\pm$ 0.65 * #	19.56 $\pm$ 3.21 * #	28.79 $\pm$ 4.32 * #

Note: Compared with before treatment, *P<0.05; Compared with the control group during the same period, #P<0.05

Comparison of baseline data between the two groups

There were no significant differences in age, gender, course of disease, WOMAC total score, VAS score and other baseline indicators between the two groups (P>0.05), which were comparable (Table 1).

Comparison of WOMAC scores between the two groups

Before treatment, there was no difference in WOMAC scores between the two groups (P>0.05). After 1-3 weeks of treatment, the scores of the two groups were significantly decreased (P<0.05), and the pain, stiffness and function scores of the observation group were significantly lower than those of the control group (P<0.05). See Table 2.

Comparison of VAS scores between the two groups

There was no difference in VAS score between the two groups before treatment (P>0.05). At 1-3 weeks after treatment, the VAS scores of the observation group were lower than those of the control group (P<0.05). See Table 3.

Assessment of medication compliance and safety

Medication adherence

The treatment compliance of the two groups was 100%, and there was no dropout case, as shown in Table 4. This indicates that sodium hyaluronate alone and combined with Zhengqing Fengtongning intra-articular injection have good patient acceptance, which may be related to the following factors:

1. Short treatment cycle (3 times / 3 weeks) and convenient operation;
2. There is no gastrointestinal adverse reaction of oral drugs, and the patient's adaptability is better.
3. Improvement of symptoms (such as pain relief) could be observed in the short term after treatment, which enhanced patients' confidence.

Safety assessment

1. Minor adverse events: swelling (2 cases) and ecchymosis (2 cases) at the injection site were the main adverse events in the control group, and 1 case of local skin temperature increase occurred in the observation group, all of which were transient reactions and could be relieved without special treatment, suggesting that adverse reactions may be related to the injection procedure rather than the drug toxicity.
2. Serious adverse events: there were no serious

complications such as joint infection and anaphylactic shock in the two groups, and there was no abnormal fluctuation of liver and kidney function indexes, which verified the safety of combined treatment.

3. Comparison between the two groups: there was no significant difference in the incidence of adverse events between the two groups (P>0.05), indicating that the addition of Zhengqing Fengtongning did not significantly increase the safety risk, and the combined regimen had comparable safety with monotherapy. Table 5 shows the above results.

Comparison of SF-36 scores between the two groups

At 3 weeks after treatment, the scores of all dimensions and the total score of SF-36 in the observation group were significantly higher than those in the control group (P<0.05). See Table 6.

Comparison of clinical effects between the two groups

The total effective rate of the observation group was 91.18%, which was significantly higher than 73.53% of the control group (P<0.05). See Table 7.

Table 3. Comparison of VAS scores between the two groups before and after treatment (mean $\pm$ standard deviation, score)

Time	Groups	Number of cases	VAS Score
Before treatment	Control group	34	7.25 $\pm$ 1.23
	Observation group	34	7.31 $\pm$ 1.19

Table 4. Medication adherence

Groups	Number of cases	Number of cases completed treatment	Number of dropouts	Compliance
Control group	34	34	0	100%
Observation group	34	34	0	100%

Table 5. Medication adherence

Types of Adverse Events	Control group (n=34)	Observation group (n=34)	χ^2 value	P-value
Swelling at the injection site	2	0	2.06	0.152
Elevated local skin temperature	0	1	1.03	0.310
Ecchymosis at the injection site	2	0	2.06	0.152
Serious adverse events (infections/allergies)	0	0	-	-

Table 6. Comparison of SF-36 scores before and after treatment between the two groups (mean $\pm$ standard deviation, scores)

Dimensions	Group of groups	Number of cases	Before treatment	3 weeks after treatment
Physiological functions	Control group	34	52.36 $\pm$ 6.54	68.54 * 7.21 mm
	Observation group	34	52.51 $\pm$ 6.48	76.32 $\pm$ 7.89 * #
Physiological functions	Control group	34	48.56 $\pm$ 5.89	65.42 * 6.54 mm
	Observation group	34	48.72 $\pm$ 5.76	73.25 $\pm$ 6.98 * #
Body pain	Control group	34	42.36 $\pm$ 5.47	60.25 * 6.12 mm
	Observation group	34	42.51 $\pm$ 5.39	68.79 $\pm$ 6.54 * #
General health	Control group	34	45.67 $\pm$ 5.12	62.34 * 6.35 mm
	Observation group	34	45.82 $\pm$ 5.08	70.56 $\pm$ 6.78 * #
Energy	Control group	34	48.78 $\pm$ 5.67	64.56 * 6.89 mm
	Observation group	34	48.92 $\pm$ 5.59	72.34 $\pm$ 7.12 * #
Social function	Control group	34	50.25 $\pm$ 5.98	66.42 * 7.21 mm
	Observation group	34	50.41 $\pm$ 5.86	74.56 $\pm$ 7.54 * #
Emotional function	Control group	34	46.54 $\pm$ 5.76	62.35 * 6.48 mm
	Observation group	34	46.71 $\pm$ 5.69	70.25 $\pm$ 6.89 * #
Mental health	Control group	34	49.21 $\pm$ 5.89	65.47 * 7.12 mm
	Observation group	34	49.36 $\pm$ 5.78	73.56 $\pm$ 7.45 * #
Total score	Control group	34	47.32 $\pm$ 5.67	63.54 * 6.89 mm
	Observation group	34	47.46 $\pm$ 5.59	71.32 $\pm$ 7.21 * #

Note: Compared with before treatment, *P<0.05; Compared with the control group during the same period, #P<0.05

Table 7. Medication adherence

Groups	Number of cases	Conspicuous effect	Effective	Ineffective	Total effective rate
Control group	34	12 (35.29)	13 (38.24)	9 (26.47)	25 (73.53)
Observation group	34	18 (52.94)	13 (38.24)	3 (8.82)	31 * (91.18)
Ecchymosis at the injection site	2	0	2.06	0.152	
Serious adverse events (infections/allergies)	0	0	-	-	

Note: Compared with the control group, *P<0.05

Discussion

As a highly prevalent degenerative joint disease, the pathogenesis of knee osteoarthritis (KOA) is complex, involving multiple factors such as cartilage degeneration, synovial inflammation, and changes in synovial fluid composition. In recent years, intra-articular injection therapy has been widely used due to its advantages of strong targeting, rapid onset of action, and few adverse reactions. By comparing the clinical effects of sodium hyaluronate alone and combined with

Zhengqing Fengtongning injection in the treatment of patients with KOA, this study aims to explore the efficacy and safety of combined drug strategy.

Molecular mechanism and synergistic effect of combined intervention

This study confirmed that sodium hyaluronate combined with Zhengqing Fengtongning intra-articular injection can optimize the treatment effect of knee osteoarthritis (KOA) through multi-target synergistic regulation. As for the molecular mechanism,

sodium hyaluronate binds to CD44 receptor on the surface of synovial cells, activates AKT/mTOR signaling pathway, promotes the synthesis of type II collagen and proteoglycan, and inhibits the expression of matrix metalloproteinase (MMP-13) and polyproteoglycan (ADAMTS-5), thereby delaying cartilage degradation[9]. Sinomenine in Zhengqingfengtongning can inhibit the phosphorylation of NF- κ B/p65, block the transcription of TNF- α , IL-1 β and other pro-inflammatory factors, and reduce the excitability of nociceptor by regulating the voltage-gated sodium channel (Nav1.7), so as to achieve central-peripheral dual analgesia[12]. The combination of the two drugs can form a synergistic effect on cartilage matrix protection (WOMAC function score in the observation group decreased by 4.76 points compared with the control group, $P < 0.05$) and inflammatory microenvironment regulation. This effect may be related to the enhancement of viscoelastic maintenance time of sodium hyaluronate by sinomenine. Sinomenine can stabilize the structure of hyaluronic acid molecular network through hydrogen bonding and prolong its joint cavity residence time [12].

Conformity of evidence-based medical evidence and guidelines for clinical efficacy

In this study, the total effective rate of the observation group was 91.18%, which was significantly higher than 73.53% of the control group ($P < 0.05$). This result echoes [13] the recommendation of "Chinese Guidelines for the Diagnosis and Treatment of Osteoarthritis (2024 Edition)" that "moderate to severe KOA can be treated with joint cavity drug combination". Comparison with previous literature: Maheu et al.'s meta-analysis showed that the effective rate of sodium hyaluronate monotherapy in the treatment of KOA was 68%-75% [10], while Huang et al.'s systematic review showed that the pain relief SMD value of Zhengqing Fengtongning monotherapy was -0.87 [12]. In this study, the synergistic effect of the combination therapy (29.3% increase in pain score reduction) was beyond the simple superposition of the single drug effect of the two drugs, suggesting the existence of synergistic effect. From the perspective of clinical decision-making, the regimen was particularly effective for patients with moderate to severe WOMAC total score > 60 (58.8% in this study). At 3 weeks after treatment, the SF-36 physiological function dimension score was increased by 7.78 points compared with the control group ($P < 0.05$). This is consistent [7] with the conclusion of Osani et al. "The improvement of function is strongly correlated with the improvement of quality of life".

Differentiated analysis with similar studies

The existing studies on the combined treatment of KOA mostly focus on the combination of sodium hyaluronate and glucocorticoids, but the latter has the risk of accelerating cartilage degradation [10]. The innovation points of this study are as follows: (1) Zhengqing Fengtongning, which has immunomodulatory properties, was used to replace glucocorticoid to avoid iatrogenic joint injury; (2) Through the dual pathway mechanism of "lubrication and protection, anti-inflammation and analgesia", the effect was superposition. At 3 weeks after treatment, the VAS score of the treatment group decreased by 1.12 points compared with the control group ($P < 0.05$), and there was no systemic reactions such as blood glucose fluctuation common to glucocorticoids. Of note, the results of this study clinically echoed the "48% increase in global KOA prevalence" reported by Long et al., suggesting the potential value of combined treatment in reducing the rate of

disability (YLD reached 18.9 million person-years globally) [2].

Study limitations and expectations

Although the results of this study are of certain reference value, they also have certain limitations. First, the sample size was relatively limited and not fully representative of the broad population. Secondly, the treatment and follow-up period was only 3 weeks, so the medium and long-term maintenance of the efficacy could not be observed. In addition, the absence of a placebo group or other positive control group limits the attribution of treatment effects.

Future studies can be improved in the following aspects: first, expand the sample size and include multi-center data to enhance the representativity and external validity of the study results; the second is to extend the follow-up period and systematically evaluate the persistence and recurrence rate of the therapeutic effect. Thirdly, the blinded design and biomarker detection were introduced to evaluate the efficacy and mechanism more objectively. In addition, the synergistic effect of combination therapy with other interventions (such as exercise therapy and rehabilitation training) is also worthy of further exploration.

Summary

In conclusion, sodium hyaluronate combined with Zhengqing Fengtongning intra-articular injection is superior to single drug therapy in relieving pain, improving function and quality of life in the treatment of KOA, and has good safety. This combined regimen provides a new effective strategy for the non-surgical treatment of KOA and is worthy of clinical application. However, more high-quality studies are still needed to further verify its efficacy and long-term safety.

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